

Listing of Claims:

This listing of claims will replace all prior versions and listings of claims in the application:

1.-49. (Cancelled)

50. (Previously Presented) A process for the preparation of a rapidly disintegrating solid dosage form capable of forming a stable suspension without irreversible particle aggregation, particle agglomeration, or particle growth, comprising the steps of:

- a) preparing an aqueous suspension including primary particles of a water insoluble or poorly water-soluble drug in the presence of one or more surface stabilizing agents, of which at least one is a phospholipid, or a combination of one or more surface stabilizing agents and one or more phospholipids, wherein the concentration of the phospholipid in the aqueous suspension ranges from about 0.1% w/w to about 90% w/w;
- b) subjecting the aqueous suspension to a particle fragmentation process to form a homogeneous aqueous suspension of micron and submicron particles, wherein the mean volume weighted particle size of the water-insoluble or poorly water-soluble drug particles in the suspension ranges between about 0.05 and about 10 micrometers;
- c) admixing the homogenous suspension of step b) with at least two rapidly dispersible matrix-forming agents said at least two rapidly dispersible matrix-forming agents, being present in an amount of between 0.1% w/w and 90% w/w of the aqueous suspension, said amount permitting a dried solid form of said suspension, upon reconstitution in an aqueous environment, to revert to a suspension having no more than about 20% by weight of particle aggregation or agglomeration compared with the amount of aggregation or agglomeration of particles comprising a pre-dried suspension;
- d) drying the admixture to produce a solid having surface stabilized drug particles dispersed and embedded throughout a support matrix formed by the at least two matrix-forming bulking/releasing agents, or combination thereof, wherein the support matrix dissolves or substantially disperses in a rapid disintegration time of less than 2 minutes upon contact between the solid and aqueous environment resulting in a release of the surface stabilized drug particles into the aqueous environment as a suspension; and further wherein, after contact between the solid and the

aqueous environment, the resulting suspension comprises no more than about 20% by weight of aggregated or agglomerated primary particles;

- e) course milling and blending the solid with one or more pharmaceutically acceptable excipients to produce a dried powder; and
- f) forming the solid or dried powder into a solid dosage form of the drug.

51. (Previously Presented) The process according to claim 50, wherein the at least two matrix-forming agents are selected from the group consisting of a pharmaceutically acceptable saccharide, a pharmaceutically acceptable polysaccharide, a pharmaceutically acceptable humectant, a pharmaceutically acceptable cellulose based polymer, combinations thereof, and combinations of these with a pH buffering salt.

52. (Previously Presented) The process according to claim 50, wherein the at least two matrix-forming agents are selected from the group consisting of mannitol, trehalose, sorbitol, maltose, sucrose, lactose and combinations thereof; combinations of mannitol, trehalose, sorbitol and maltose with lactose; combinations of mannitol, trehalose, sorbitol, maltose, and lactose with sucrose; microcrystalline cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, methylcellulose and combinations thereof; and combinations thereof with a pH buffering salt.

53. (Cancelled)

54. (Previously Presented) The process according to claim 50, wherein the at least two matrix-forming agents are present in an amount between 0.5% w/w and 50% w/w of the aqueous suspension.

55. (Cancelled)

56. (Previously presented) The process according to claim 50, wherein the water-insoluble or poorly water-soluble drug is selected from the group consisting of antifungal agents, immunosuppressive agents, immunoactive agents, antiviral agents, antineoplastic agents, analgesic agents, anti-inflammatory agents, antibiotic agents, antiepileptic agents, anesthetic agents, hypnotic agents, sedative agents, antipsychotic agents, neuroleptic agents, antidepressant agents, anxiolytic agents, anticonvulsant agents, antagonist agents, neuron blocking agents, anticholinergic agents,

cholinomimetic agents, antimuscarinic agents, muscarinic agents, anti adrenergic agents, antiarrhythmic agents, antihypertensive agents, hormones, and nutrients.

57. (Previously presented) The process according to claim 50, wherein the drug is selected from the group consisting of fenofibrate, itraconazole, and cyclosporine.

58. (Previously presented) The process according to claim 50, wherein the drug is present in an amount between 0.1 % w/w and 60% w/w of the aqueous suspension.

59. (Previously presented) The process according to claim 50, wherein the phospholipid is selected from the group consisting of an egg phospholipid, a soybean phospholipid, and combinations thereof.

60. (Previously presented) The process according to claim 50, wherein the phospholipid is selected from the group consisting of hydrogenated phospholipid, partially hydrogenated phospholipid, and combinations thereof.

61. (Previously presented) The process according to claim 50, wherein the phospholipid is selected from the group consisting of phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, phosphatidic acid, a lysophospholipid, and combinations thereof.

62. (Previously presented) The process according to claim 50, wherein the surface stabilizing agent is selected from the group consisting of pharmaceutically acceptable nonionic surfactants, pharmaceutically acceptable anionic surfactants, and pharmaceutically acceptable cationic surfactants.

63 (Previously presented) The process according to claim 50, wherein the surface stabilizing agent is selected from the group consisting of casein, gelatin, tragacanth, acacia, and combinations thereof.

64. (Previously presented) The process according to claim 50, wherein the surface stabilizing agent is selected from the group consisting of a pharmaceutically acceptable polyoxyethylene fatty

alcohol ether, a sorbitan fatty acid ester, a polyoxyethylene fatty acid ester, a poloxamer, a polaxamine, and combinations thereof.

65. (Previously presented) The process according to claim 50, wherein the surface stabilizing agent is selected from the group consisting of glycerol monostearate, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, and combinations thereof.

66. (Previously presented) The process according to claim 50, wherein the surface stabilizing agent is selected from the group consisting of potassium laurate, triethanolamine stearate, sodium lauryl sulfate, an alkyl polyoxyethylene sulfate, sodium alginate, sodium deoxycholate, dioctyl sodium sulfosuccinate, a negatively charged glyceryl ester, sodium carboxymethylcellulose, calcium carboxymethylcellulose, and combinations thereof.

67. (Previously presented) The process according to claim 50, wherein the surface stabilizing agent is selected from the group consisting of benzalkonium chloride, cetyltrimethylammonium bromide, lauryldimethylbenzylammonium chloride, and combinations thereof.

68. (Previously presented) The process according to claim 50, wherein the surface stabilizing agent is present in an amount between 0.5% w/w and 50% w/w of the aqueous suspension.

69. (Previously presented) The process according to claim 50, wherein the admixture is dried by spray drying, spray coating, or freeze-drying.

70. (Previously presented) The process according to claim 50, wherein the particle fragmentation process is selected from the group consisting of sonication, milling, homogenization, microfluidization, antisolvent precipitation and solvent precipitation.

71. (Previously presented) The process according to claim 50, wherein the pharmaceutically acceptable excipient is a tableting aid for compression, a glidant for hard gelatin encapsulation, an effervescent disintegration agent, a dispersant for a dry powder inhaler, or a combination thereof.

72. (Previously presented) The process according to claim 50, wherein the dosage form is a tablet, a gelatin encapsulation, or a powder.

73. (Previously Presented) A process for the preparation of a rapidly disintegrating solid dosage form capable of forming a stable suspension without irreversible particle aggregation, particle agglomeration or particle growth comprising the steps of:

- a) admixing at least two matrix-forming agents with an aqueous homogeneous suspension including solid drug particles onto which is adsorbed at least one surface stabilizing agent of which one is a phospholipid, or a combination of one or more surface stabilizing agents and one or more phospholipids, wherein the aqueous homogeneous suspension is prepared with a water insoluble or poorly water-soluble drug in the presence of one or more surface stabilizing agents, of which at least one is a phospholipid and is subjected to a particle fragmentation process resulting in a suspension of micron and submicron particles, wherein the mean volume weighted particle size of the water-insoluble or poorly water-soluble drug particles in the suspension ranges between about 0.05 and about 10 micrometers, and further wherein said at least two rapidly dispersible matrix-forming bulking/releasing agents, or said combination of matrix-forming bulking agent and matrix-forming releasing agent, are present in an amount of between 0.1% w/w and 90% w/w of the aqueous suspension, said amount permitting a dried solid form of said suspension, upon reconstitution in an aqueous environment, to revert to a suspension having no more than about 20% by weight of particle aggregation or agglomeration compared with the amount of aggregation or agglomeration of particles comprising a pre-dried suspension;
- b) distributing the admixture of step (a) into unit dosage form molds; and
- c) freeze-drying said admixture in said unit dosage form molds to produce a solid dosage form of the surface stabilized drug particles dispersed and embedded throughout a support matrix of said matrix-forming agent or agents, wherein said matrix dissolves or substantially disperses in a rapid disintegration time of less than 2 minutes upon contact with an aqueous environment to release the surface stabilized drug particles into the aqueous environment as a suspension; and further after contact between the solid and the aqueous environment, the resulting suspension comprises no more than 20% by weight of aggregated or agglomerated primary particles.

74. (Previously Presented) The process according to claim 73, wherein the at least two matrix-forming agents are selected from the group consisting of a pharmaceutically acceptable saccharide, a

pharmaceutically acceptable polysaccharide; a pharmaceutically acceptable humectant a pharmaceutically acceptable cellulose based polymer, combinations thereof, and combinations of these with a pH buffering salt.

75. (Previously Presented) The process according to claim 73, wherein the at least two matrix-forming agents are selected from the group consisting of mannitol, trehalose, sorbitol, maltose, sucrose, lactose and combinations thereof; combinations of mannitol, trehalose, sorbitol and maltose with lactose; combinations of mannitol, trehalose, sorbitol, maltose and lactose with sucrose; microcrystalline cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, methylcellulose and combinations thereof; and combinations thereof with a pH buffering salt.

76. (Cancelled)

77. (Previously Presented) The process according to claim 73, wherein the at least two matrix-forming agents are present in an amount between 0.5% w/w and 50% w/w of the aqueous suspension.

78. (Canceled)

79. (Previously presented) The process according to claim 73, wherein the water insoluble or poorly water-soluble drug is selected from the group consisting of antifungal agents, immunosuppressive agents, immunoactive agents, antiviral agents, antineoplastic agents, analgesic agents, anti-inflammatory agents, antibiotic agents, antiepileptic agents, anesthetic agents, hypnotic agents, sedative agents, antipsychotic agents, neuroleptic agents, antidepressant agents, anxiolytic agents, anticonvulsant agents, antagonist agents, neuron blocking agents, anticholinergic agents, cholinomimetic agents, antimuscarinic agents, muscarinic agents, anti adrenergic agents, antiarrhythmic agents, antihypertensive agents, hormones, and nutrients.

80. (Previously presented) The process according to claim 73, wherein the drug is fenofibrate, itraconazole, or cyclosporine.

81. (Previously presented) The process according to claim 73, wherein the drug is present in an amount between 0.1 % w/w and 60% w/w of the aqueous suspension.

82. (Previously presented) The process according to claim 73, wherein the phospholipid is selected from the group consisting of an egg phospholipid, a soybean phospholipid, and combinations thereof.

83. (Previously presented) The process according to claim 73, wherein the phospholipid is selected from the group consisting of hydrogenated phospholipid, partially hydrogenated phospholipid, and combinations thereof.

84. (Previously presented) The process according to claim 73, wherein the phospholipid is selected from the group consisting of phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, phosphatidic acid, a lysophospholipid, and combinations thereof.

85. (Previously presented) The process according to claim 73, wherein the surface modifying agent is selected from the group consisting of pharmaceutically acceptable nonionic surfactants, pharmaceutically acceptable anionic surfactants, and pharmaceutically acceptable cationic surfactants.

86. (Previously presented) The process according to claim 73, wherein the surface modifying agent is selected from the group consisting of casein, gelatin, tragacanth, acacia, and combinations thereof.

87. (Previously presented) The process according to claim 73, wherein the surface modifying agent is selected from the group consisting of a pharmaceutically acceptable polyoxyethylene fatty alcohol ether, a sorbitan fatty acid ester, a polyoxyethylene fatty acid ester, a poloxamer, a polaxamine, and combinations thereof.

88. (Previously presented) The process according to claim 73, wherein the surface modifying agent is selected from the group consisting of glycerol monostearate, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, and combinations thereof.

89. (Previously presented) The process according to claim 73, wherein the surface modifying agent is selected from the group consisting of potassium laurate, triethanolamine stearate, sodium

lauryl sulfate, an alkyl polyoxyethylene sulfate, sodium alginate, sodium deoxycholate, dioctyl sodium sulfosuccinate, a negatively charged glyceryl ester, sodium carboxymethylcellulose, calcium carboxymethylcellulose, and combinations thereof.

90. (Previously presented) The process according to claim 73, wherein the surface modifying agent is selected from the group consisting of benzalkonium chloride, cetyltrimethylammonium bromide, lauryldimethylbenzylammonium chloride, and combinations thereof.

91. (Previously presented) The process according to claim 73, wherein the surface modifying agent is present in an amount between 0.5% w/w and 50% w/w of the aqueous suspension.

92. (Previously presented) The process according to claim 73, wherein the particle fragmentation process is selected from the group consisting of sonication, milling, homogenization, microfluidization, antisolvent precipitation and solvent precipitation.

93. (Previously presented) The process according to claim 73, wherein the dosage form is a tablet.

94. (Original) A dosage form prepared by the process of claim 50.

95. (Original) A dosage form prepared by the process of claim 73.

96. (Canceled)

97. (Previously Presented) A process for the preparation of a rapidly disintegrating solid dosage form capable of forming a stable suspension without irreversible particle aggregation, particle agglomeration, or particle growth, comprising the steps of:

a) preparing an aqueous suspension including a water insoluble or poorly water-soluble drug in the presence of one or more surface stabilizing agents, of which at least one is a phospholipid, or a combination of one or more surface stabilizing agents and one or more phospholipids, wherein the concentration of the phospholipid in the aqueous suspension ranges from about 0.1% w/w to about 90% w/w;

b) admixing the aqueous suspension of step a) with at least two rapidly dispersible matrix-forming agents, said at least two rapidly dispersible matrix-forming agents, being present in an amount of between 0.1% w/w and 90% w/w of the aqueous suspension, said amount permitting a dried solid form of said suspension, upon reconstitution in an aqueous environment, to revert to a suspension having no more than about 20% by weight of particle aggregation or agglomeration compared with the amount of aggregation or agglomeration of particles comprising a pre-dried suspension;

c) subjecting the aqueous suspension to a particle fragmentation process to form a homogeneous aqueous suspension of micron and submicron particles, wherein the mean volume weighted particle size of the water-insoluble or poorly water-soluble drug particles in the suspension ranges between about 0.05 and about 10 micrometers;

d) drying the homogeneous suspension of step c) to produce a solid having surface stabilized drug particles dispersed and embedded throughout a support matrix formed by the at least two matrix-forming agents, or combination thereof;

wherein the support matrix dissolves or substantially disperses in a rapid disintegration time of less than 2 minutes upon contact between the solid and aqueous environment resulting in a release of the surface stabilized drug particles into the aqueous environment as a suspension; and further wherein, after contact between the solid and the aqueous environment, the resulting suspension comprises no more than 20% by weight of aggregated or agglomerated primary particles;

e) optionally course milling and blending the solid with one or more pharmaceutically acceptable excipients to produce a dried powder; and

f) forming the solid or dried powder into a solid dosage form of the drug.

98. (Previously Presented) A process for the preparation of a rapidly disintegrating solid dosage form capable of forming a stable suspension without irreversible particle aggregation, particle agglomeration, or particle growth, comprising the steps of:

a) preparing an aqueous suspension including a water insoluble or poorly water-soluble drug selected from the group consisting of cyclosporine, itraconazole and fenofibrate, in the presence of one or more surface stabilizing agents selected from the group consisting of Myrij™ 52, polyvinyl pyrrolidone (PVP 17), sodium deoxycholate, TWEEN™ 80 and a

combination thereof, and further including at least one phospholipid selected from the group consisting of phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, phosphatidic acid, a lysophospholipid, and combinations thereof; wherein the concentration of the phospholipid in the aqueous suspension ranges from about 0.1% w/w to about 90% w/w;

b) subjecting the aqueous suspension of step a) to a particle fragmentation process to form a homogeneous aqueous suspension of micron and submicron particles, wherein the mean volume weighted particle size of the water-insoluble or poorly water-soluble drug particles in the suspension ranges between about 0.05 and about 10 micrometers;

c) admixing the homogenous suspension of step b) with at least two rapidly dispersible matrix-forming agents, said at least two matrix-forming agents selected from the group consisting of sucrose, lactose, trehalose, mannitol, sorbitol and a combination thereof, said at least two rapidly dispersible matrix-forming agents, being present in an amount of between 0.1% w/w and 90% w/w of the aqueous suspension, said amount permitting a dried solid form of said suspension, upon reconstitution in an aqueous environment, to revert to a suspension having no more than about 20% by weight of particle aggregation or agglomeration compared with the amount of aggregation or agglomeration of particles comprising a pre-dried suspension;

d) drying the admixture to produce a solid having surface stabilized drug particles dispersed and embedded throughout a support matrix formed by the at least two matrix-forming bulking/releasing agents, or combination thereof;

wherein the support matrix dissolves or substantially disperses in a rapid disintegration time of less than 2 minutes upon contact between the solid and aqueous environment resulting in a release of the surface stabilized drug particles into the aqueous environment as a suspension; and further wherein, after contact between the solid and the aqueous environment, the resulting suspension comprises no more than 20% by weight of aggregated or agglomerated primary particles;

e) optionally course milling and blending the solid with one or more pharmaceutically acceptable excipients to produce a dried powder; and

f) forming the solid or dried powder into a solid dosage form of the drug.

99. (Previously presented) The process according to any one of claims 50, 73, 97, or 98, wherein, in step d), said reconstituted suspension comprises no more than 10% by weight of aggregated primary particles.

100. (Previously presented) The process according to any one of claims 50, 73, 97, or 98, wherein, in step d), said reconstituted suspension comprises no more than 1% by weight of aggregated primary particles.

101. (Previously presented) A dosage form prepared by the process of claim 97.

102. (Previously presented) A dosage form prepared by the process of claim 98.

103. (Previously Presented) The process according to claim 97, wherein the at least two matrix-forming agents are selected from the group consisting of a pharmaceutically acceptable saccharide, a pharmaceutically acceptable polysaccharide, a pharmaceutically acceptable humectant, a pharmaceutically acceptable cellulose based polymer, combinations thereof, and combinations of these with a pH buffering salt.

104. (Previously Presented) The process according to claim 50, wherein the at least two matrix-forming agents are selected from the group consisting of mannitol, trehalose, sorbitol, maltose and combinations thereof; combinations of mannitol, trehalose, sorbitol and maltose with lactose; combinations of mannitol, trehalose, sorbitol, maltose, and lactose with sucrose; microcrystalline cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, methylcellulose and combinations thereof; and combinations thereof with a pH buffering salt.

105.-107. (Cancelled)

108. (Previously presented) The process according to claim 97, wherein the water-insoluble or poorly water-soluble drug is selected from the group consisting of antifungal agents, immunosuppressive agents, immunoactive agents, antiviral agents, antineoplastic agents, analgesic agents, anti-inflammatory agents, antibiotic agents, antiepileptic agents, anesthetic agents, hypnotic agents, sedative agents, antipsychotic agents, neuroleptic agents, antidepressant agents, anxiolytic agents, anticonvulsant agents, antagonist agents, neuron blocking agents, anticholinergic agents,

cholinomimetic agents, antimuscarinic agents, muscarinic agents, anti adrenergic agents, antiarrhythmic agents, antihypertensive agents, hormones, and nutrients.

109. (Previously presented) The process according to claim 97, wherein the drug is selected from the group consisting of fenofibrate, itraconazole, and cyclosporine.

110. (Previously presented) The process according to claim 97 or claim 98, wherein the drug is present in an amount between 0.1 % w/w and 60% w/w of the aqueous suspension.

111. (Previously presented) The process according to claim 97, wherein the phospholipid is selected from the group consisting of an egg phospholipid, a soybean phospholipid, and combinations thereof.

112. (Previously presented) The process according to claim 97, wherein the phospholipid is selected from the group consisting of hydrogenated phospholipid, partially hydrogenated phospholipid, and combinations thereof.

113. (Previously presented) The process according to claim 97, wherein the phospholipid is selected from the group consisting of phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, phosphatidic acid, a lysophospholipid, and combinations thereof.

114. (Previously presented) The process according to claim 97, wherein the surface stabilizing agent is selected from the group consisting of pharmaceutically acceptable nonionic surfactants, pharmaceutically acceptable anionic surfactants, and pharmaceutically acceptable cationic surfactants.

115. (Previously presented) The process according to claim 97, wherein the surface stabilizing agent is selected from the group consisting of casein, gelatin, tragacanth, acacia, and combinations thereof.

116. (Previously presented) The process according to claim 97, wherein the surface stabilizing agent is selected from the group consisting of a pharmaceutically acceptable polyoxyethylene fatty

alcohol ether, a sorbitan fatty acid ester, a polyoxyethylene fatty acid ester, a poloxamer, a polaxamine, and combinations thereof.

117. (Previously presented) The process according to claim 97, wherein the surface stabilizing agent is selected from the group consisting of glycerol monostearate, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, and combinations thereof.

118. (Previously presented) The process according to claim 97, wherein the surface stabilizing agent is selected from the group consisting of potassium laurate, triethanolamine stearate, sodium lauryl sulfate, an alkyl polyoxyethylene sulfate, sodium alginate, sodium deoxycholate, dioctyl sodium sulfosuccinate, a negatively charged glyceryl ester, sodium carboxymethylcellulose, calcium carboxymethylcellulose, and combinations thereof.

119. (Previously presented) The process according to claim 97, wherein the surface stabilizing agent is selected from the group consisting of benzalkonium chloride, cetyltrimethylammonium bromide, lauryldimethylbenzylammonium chloride, and combinations thereof.

120. (Previously presented) The process according to claim 97, wherein the surface stabilizing agent is present in an amount between 0.5% w/w and 50% w/w of the aqueous suspension.

121. (Previously presented) The process according to claim 97 or claim 98, wherein, in step d), the admixture is dried by spray drying, spray coating, or freeze-drying.

122. (Previously presented) The process according to claim 97 or claim 98, wherein the particle fragmentation process is selected from the group consisting of sonication, milling, homogenization, microfluidization, antisolvent precipitation and solvent precipitation.

123. (Previously presented) The process according to claim 97 or claim 98, wherein the pharmaceutically acceptable excipient is a tableting aid for compression, a glidant for hard gelatin encapsulation, an effervescent disintegration agent, a dispersant for a dry powder inhaler, or a combination thereof.

Parikh
USSN: 09/443,863

124. (Previously presented) The process according to claim 97 or claim 98, wherein the dosage form is a tablet, a gelatin encapsulation, or a powder.

125. (Previously presented) The process according to claim 50, wherein, in step c), said suspension has no more than about 10% by weight of particle aggregation or agglomeration compared with the amount of aggregation or agglomeration of particles comprising a pre-dried suspension.

126 (Previously presented) The process according to claim 73, wherein, in step a), said suspension has no more than about 10% by weight of particle aggregation or agglomeration compared with the amount of aggregation or agglomeration of particles comprising a pre-dried suspension.

127. (Previously presented) The process according to claim 97, wherein, in step b), said suspension has no more than about 10% by weight of particle aggregation or agglomeration compared with the amount of aggregation or agglomeration of particles comprising a pre-dried suspension.

128. (Previously presented) The process according to claim 98 wherein, in step c), said suspension has no more than about 10% by weight of particle aggregation or agglomeration compared with the amount of aggregation or agglomeration of particles comprising a pre-dried suspension.

129. (Previously presented) The process according to claim 57, wherein the drug is fenofibrate.

130. (Previously presented) The process according to claim 80, wherein the drug is fenofibrate.

131. (Previously presented) The process according to claim 109, wherein the drug is fenofibrate.